

REMARKS

Claims 1-8 are pending in this application. Claims 9-13 are cancelled without prejudice.

As a preliminary matter, the Office Action repeatedly refers to SEQ ID NO: 1 as a limitation of the present claims. Applicants assume that this is a typographical error in the Office Action, since the present claims refer to SEQ ID NO: 2, not to SEQ ID NO: 1. The arguments presented below are made on the assumption that all references to SEQ ID NO: 1 were intended to refer to SEQ ID NO: 2.

All of the Present Claims are Entitled to an August 14, 1998 Priority Date.

The Office Action indicated that an English language translation of the German priority application and a declaration under Rule 132 could be used to overcome rejections based on the Zabel *et al.* reference. Submitted herewith is a certified English translation of the German priority Application DE 198 37 015.6. The text of the translated priority application is substantially the same as the text of the present application. Accordingly, all of the present claims are amply supported by the priority application and are entitled to a priority date of August 14, 1998.

The "Declaration Under 37 CFR 132" by inventor Ulrike Zabel, submitted herewith states that Dr. Zabel is a coinventor of the invention described in the present application, along with Harald Schmidt and Wolfgang Poller. Dr. Zabel further states that she and Harald Schmidt were coauthors of Zabel *et al.*, along with Monica Wagner and Mylinh La. As attested in the Declaration, Monica Wagner was an assistant who worked under the direction of Dr. Zabel and Mylinh La was a student who worked under the guidance of Dr. Schmidt. Neither Monica Wagner nor Mylinh La made an inventive contribution to the claims of the present application. Zabel *et al.* is the work of the present inventors and was published after the priority date of the present application. Accordingly, Zabel *et al.* is not available as a reference against the present claims.

Claims 1 and 2 Are Not Anticipated by the Applied References.

Claim 1 has been rejected as allegedly being anticipated by Giuili *et al.* This rejection is unwarranted and should be withdrawn. Claim 1 is directed to an isolated human guanylyl cyclase α 1/ β 1 protein, which is an enzymatically active heterodimer comprising hsGCo1 (having the amino acid sequence of SEQ ID NO: 2) and hsGC β 1 (having the amino acid sequence of SEQ ID NO: 4). Although Giuili *et al.* purport to describe certain α and β

subunits of human guanylyl cyclase, the reference does not describe an enzymatically active heterodimer of hsGC α 1 (SEQ ID NO: 2) and hsGC β 1 (SEQ ID NO: 4). In fact, the sequence for the α chain reported by the reference (see Fig. 2 of Giuili *et al.*) is not the same sequence as SEQ ID NO: 2 of the present application. The amino acid sequence for the α chain in Fig. 2 of Giuili *et al.* includes 717 amino acid residues, whereas SEQ ID NO: 2 includes only 690 residues. Thus, the protein structure reported by Giuili, *et al.* is not the same as the isolated protein of the present claims. Sequence in Fig. 2 of Giuili *et al.* includes a number of specific sequence differences from SEQ ID NO: 2 beginning with amino acid residue 124 and continuing through the end of the sequence. Accordingly, Giuili *et al.* does not teach or suggest the isolated human guanylyl cyclase α 1/ β 1 protein that is presently claimed.

The specific sequence differences between SEQ ID NO: 2 and the Giuili *et al.* sequence are also highlighted in Gencore sequence matching printout for "Result 1" included with the Office Action. In this printout the differences between the database sequence and the Giuili *et al.* sequence are listed as "CONFLICTS". The sequence in the database clearly is NOT the same sequence as reported by Giuili *et al.* in Fig. 2. Furthermore, Giuili *et al.* isolated and sequenced a DNA molecule, not a protein. The present claims are directed to an isolated protein. Clearly, Giuili *et al.* does not disclose an isolated protein having the amino acid residue sequence of SEQ ID NO: 2, and thus, does not disclose all of the limitations of claim 1. Accordingly, Giuili *et al.* cannot anticipate claim 1 of the present application.

The Gencore printout bearing a date of July 2, 2003 also shows that the database sequence, for which the Examiner obtained a 100% match with SEQ ID NO: 2, was modified on May 30, 2000, which is after the priority date of the present application. Thus, this database sequence cannot be used as a reference against the present application. A copy of the Genecore printout with the relevant portions underlined, and a copy of page 85 of Giuili *et al.* with the sequence differences underlined, are attached hereto as Appendix I and Appendix II, respectively, for the convenience of the Examiner.

Claim 1 and 2 were also rejected as being anticipated by Zabel *et al.* Since Zabel *et al.* is not available as a reference against this application , this ground for rejection is moot.

Claims 3-8 Are Not Obvious Over the Applied References.

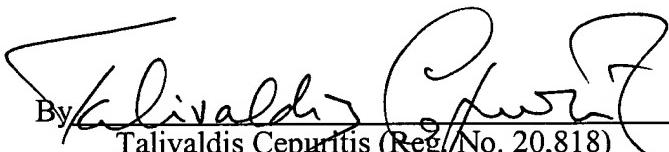
Claims 3-8 have been rejected as purportedly being obvious over either Zabel *et al.* or Giuili *et al.* and further in view of common knowledge in the art regarding methods of affinity chromatography using affinity tags for protein purification. This rejection is also

unwarranted, and is hereby traversed. As noted above, Zabel *et al.* is not available as a reference against the present application. Giuli *et al.* does not teach or suggest an isolated protein having the amino acid residue sequence of SEQ ID NO: 2 as explained hereinabove, which is a material limitation of all of the claims. Accordingly, even assuming common knowledge regarding purification using affinity tags, the combination of Giuli *et al.* with such common knowledge cannot and does not render claims 3-8 obvious. The issue here is not purification, but rather whether or not the claimed isolated protein would have been obvious to one of ordinary skill in the art. A *prima facie* case for obviousness has not been established. The obviousness rejection cannot stand.

Conclusion.

All of the present claims are deemed to be patentable over Giuli *et al.* Reconsideration and entry of this amendment are earnestly solicited. In the event that the foregoing is not deemed persuasive, Applicants request that this amendment be entered to place the application in better form for appeal.

Respectfully submitted,

By 
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Dated August 2, 2004

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Application No. 09/762,767

Amendment Dated: August 2, 2004

APPENDIX I

Pages 1 and 2 of Gencore Search Report labeled "us-09-762-767a-2.rsp" (provided with the Office Action), with underlining added by Applicants to point out significant information in the report relating differences between the database sequence and the sequence of Giuli *et al.*

GenCore version 5.1.6
Copyright (c) 1993 - 2003 Compugen Ltd.

OM protein - protein search, using sw model

Run on: June 27, 2003, 12:55:07 ; Search time 11.0695 Seconds
(without alignments)

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : SwissProt_40;*

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 112892 seqs, 41476328 residues
total number of hits satisfying chosen parameters: 112992

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : SwissProt_40;*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	Query	Match	Length	DB	ID	Description
1	3593	100.0	690	1	CYG3_HUMAN	Q02108	homo sapien
2	3232	90.0	690	1	CYGD_BOVIN	P16686	rattus norvegicus
3	3107.5	86.5	691	1	CYGD_BOVIN	P16687	bos taurus
4	1651	46.0	730	1	CYGD_BOVIN	Q9WV11	rattus norvegicus
5	1635	45.5	732	1	CYGD_HUMAN	P33102	homo sapien
6	976.5	27.2	683	1	CYGD_DROME	Q07093	drosophilapharallela
7	795	22.1	619	1	CYGD_BOVIN	P20595	rattus norvegicus
8	793.5	22.1	619	1	CYGD_BOVIN	P16068	bos taurus
9	789.5	22.0	619	1	CYGL_HUMAN	Q02153	homo sapien
10	774.5	21.6	682	1	CYGD_BOVIN	P22217	rattus norvegicus
11	708	19.7	617	1	CYGD_HUMAN	Q7543	homo sapien
12	460	12.8	1047	1	ANPB_BOVIN	P46197	bos taurus
13	460	12.8	1047	1	ANPB_HUMAN	P20594	homo sapien
14	460	12.8	1047	1	ANPB_BOVIN	P16067	rattus norvegicus
15	457.5	12.7	1057	1	ANPA_BOVIN	P18910	rattus norvegicus
16	456.5	12.7	1061	1	ANPA_HUMAN	P16066	homo sapien
17	454.5	12.6	1057	1	ANPA_BOVIN	P18293	mus musculus
18	452	12.6	433	1	KSGC_BOVIN	P55205	rattus norvegicus
19	450	12.5	1108	1	CYGE_BOVIN	P52285	mus musculus
20	448	12.4	1108	1	CYGE_BOVIN	P18140	rattus norvegicus
21	445	12.3	1108	1	CYGD_CANFA	O19179	canis familiaris
22	442	12.2	1103	1	CYGP_HUMAN	P51841	homo sapien
23	440	12.2	1108	1	CYGR_BOVIN	P02740	bos taurus
24	438	12.2	1108	1	CYGR_BOVIN	P55203	bos taurus
25	438	12.2	1110	1	CYGD_BOVIN	Q02846	homo sapien
26	434	12.1	1103	1	CYGD_HUMAN	P51839	rattus norvegicus
27	430	12.0	1110	1	CYGX_BOVIN	P55202	anguilla japonica
28	428.5	11.9	1050	1	ANPB_BOVINA	P16065	strongylus
29	427	11.9	1125	1	HSER_BOVINA	P55204	sus scrofa
30	414.5	11.5	1073	1	HSER_PIG	P25092	homo sapien
31	408.5	11.4	1073	1	HSER_HUMAN	P23897	rattus norvegicus
32	407.5	11.3	1072	1	HSER_BOVINA	P70106	cavia porcellus
33	399.5	11.1	1076	1	HSER_CAVPO		

ALIGNMENTS

RESULT 1		CYG3_HUMAN		STANDARD		PRT;		690 AA.	
ID	CG3_HUMAN	AC	Q02108; O43843; 1	DT	01-JUL-1993 (Rel. 26. Created.)	DT	30-MAY-2000 (Rel. 39. Last sequence update.)	DT	16-OCT-2001 (Rel. 40. Last annotation update)
AC	Q02108; O43843; 1	DT	01-JUL-1993 (Rel. 39. Last sequence update.)	DT	16-OCT-2001 (Rel. 40. Last annotation update)	DE	Guanylate cyclase soluble, alpha-1 chain (EC 4.6.1.2) (GCS-alpha-1)	DE	(Soluble guanylate cyclase, large subunit) (GCS-alpha-3).
GN	GUCL1 OR GUCL1A3 OR GUCL1A3 OR GUCSA3.	OS	Homo sapiens (Human)	OS	Bukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.	OC		OC	
OC		NCBI_TAXID	9606; 1	RN	[1]	RP	SEQUENCE FROM N.A.	RN	SEQUENCE FROM N.A.
NCBI_TAXID	9606; 1	RC	TISSUE-BRAIN	RC	TISSUE-KIDNEY	RA	Ganssemans Y.; Brouckaert P.; Fiers W.; Guilleaen G.;	RA	MEDLINE-9216204; PubMed-1352257;
		RC		RC		RA	"Human soluble guanylate cyclase large subunit mRNA, alpha3-like."	RA	Giulii G.; Scholl U.; Bulle F.;
		RT		RT		RT	"Molecular cloning of the cDNAs coding for the two subunits of soluble guanylyl cyclase from human brain."	RT	PubMed-1352257;
		RT		RT		RL	soluble guanylyl cyclase from human brain."	RL	PNAS Lett. 304:83-88(1992).
		RL		RL		RN		RN	
		SEQUENCE FROM N.A.		SEQUENCE FROM N.A.		RP		SEQUENCE FROM N.A.	
		RC		RC		RC		RC	
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DR	EMBL; Y15723; CAA75738.1; -.	Db	661 QQGTNSKPCQQKKDVGDNANFLGKASGID 690
DR	PIR; S23098; S23098.	DR	
DR	HSSP; P19687; IAWN.	DR	
DR	Gene: HGENC:4685; GUCLY1A3.	DR	
DR	MM: 139396; -.	DR	
DR	InterPro: IPR001054; G_cyclase.	RESULT 2	
PFam;	Pf00211; guanylate_cyc_1.	CG3_RAT	
SMART;	SM00044; CRCC_1.	ID	CYG3_RAT
PROSITE;	PS50125; GUANYLATE_CYLCLASES_1; 1.	AC	P19686;
KW	Lyase; cMP synthetase; Multigene family.	DT	01-FEB-1991 (Rel. 17, Created)
PROSITE;	PS50125; GUANYLATE_CYLCLASES_2; 1.	DT	01-FEB-1991 (Rel. 17, Last annotation update)
FT	AGVY -> QOS (IN REF. 1).	DT	16-OCT-2001 (Rel. 40, Last annotation update)
CONFLICT	124 481 608 GUANYLATE CYCLASE.	DE	Guanylate cyclase soluble, alpha-1 chain (EC 4.6.1.2) (GCS-alpha-1)
CONFLICT	127 131 184 VIKSTIGEVKPKCYEDEDNLGVGGTIPKDFLNSFSTLKKSSHQERKGR -> LSKNLYTKRFKLYVTRKMKTSGLW	GN	(Soluble guanylate cyclase large subunit).
FT	LEAPLSPPLQYSETDPLPRRKKGQ (IN REF. 1).	OS	Rattus norvegicus (Rat).
FT	MISSING (IN REF. 1).	OC	Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Rattus.
FT	GDATCVA -> AMP[LYL] (IN REF. 1).	OX	NCBI_TAXID=10116;
FT	GNNANFLGKASGID -> ASQFFRSTIRHNLATVAPIYKSLG	RN	
FT	DSFLKMKCRASESTGIVDG (IN REF. 1).	RP	SEQUENCE FROM N.A., AND PARTIAL SEQUENCE.
SQ	SEQUENCE 690 AA; 77452 MW; DAIE145E1145ICF CRC64;	RC	TISSUE=Lung; MEDLINE=91009100; PubMed=1698769;
Query Match	Best Local Similarity 100.0%; Score 3593; DB 1; Length 690;	RX	Nakane M., Arai K., Saeki S., Kuno T., Buechler W., Murad F.;
Matches	690; Conservate 0; N mismatches 0; Indels 0; Gaps 0;	RA	"Molecular cloning and expression of cDNAs coding for soluble guanylate cyclase from rat lung." J. Biol. Chem. 265:16841-16845(1990).
QY	1 MFCTKLKDKitGCPFSLLAPGQPVNESSSEAGSSECKATVPIQDIPENIQUESTP 60	RN	[2]
Db	1 MFCTKLKDKitGCPFSLLAPGQPVNESSSEAGSSECKATVPIQDIPENIQUESTP 60	RP	SEQUENCE FROM N.A.
QY	61 QRKTSRSRVTHTLAESICKLIFPFERVLVALQTLTAKHKIKERSRSKLEREDEFEKTAE 120	RC	STRAIN=Sprague-Dawley; TISSUE=Striatum;
Db	61 QRKTSRSRVTHTLAESICKLIFPFERVLVALQTLTAKHKIKERSRSKLEREDEFEKTAE 120	RX	SMidzinski R.M., Levitt P.; MEDLINE=9711525; PubMed=8997507;
QY	121 QAVAGGPV[E]KISEEFKICYEDEDNLGVGGTDELNSESTLQKQSHCQERG 180	RA	The alpha 1 subunit of soluble guanylyl cyclase is expressed primarily in the rat brain.".
Db	121 QAVAGGPV[E]KISEEFKICYEDEDNLGVGGTDELNSESTLQKQSHCQERG 180	RT	Brain Res. Dev. Brain Res. 97:226-234(1996).
QY	181 KRG[LEDASITCLDKEDDFLHVYYFFPKRITSLPLGIKAARAVLYETEVESLMLPPCF 240	RL	-CATALYTIC ACTIVITY: GTP = 3', 5'-cyclic GMP + diphosphate.
Db	181 KRG[LEDASITCLDKEDDFLHVYYFFPKRITSLPLGIKAARAVLYETEVESLMLPPCF 240	CC	-ENZYME REGULATION: ACTIVATED BY NITRIC OXIDE IN THE PRESENCE OF MAGNESIUM OR MANGANESE IONS.
QY	241 HNDCSFVNQPYLLSVHMKSTKPSLSPSKPOSSLVIPTSLFECKTFEPFHMFDKMTLQ 300	CC	-SUBUNIT: HEPEROIDIMER OF AN ALPHA AND A BETA CHAIN.
Db	241 HNDCSFVNQPYLLSVHMKSTKPSLSPSKPOSSLVIPTSLFECKTFEPFHMFDKMTLQ 300	CC	-CELLULAR LOCATION: Cyttoplasmic.
QY	301 FGNG[TRRLMARRDFOCKPNPEEYFELTPKINOPSGIIMLNQVIVYVRMDNSVKS 360	CC	- MISCELLANEOUS: THERE ARE TWO TYPES OF GUANYLATE CYCLASES: SOLUBLE FORMS AND MEMBRANE-ASSOCIATED RECEPTOR FORMS.
Db	301 FGNG[TRRLMARRDFOCKPNPEEYFELTPKINOPSGIIMLNQVIVYVRMDNSVKS 360	CC	- SIMILARITY: BELONGS TO ADENYL CYCLASE CLASS-4/GUANYL CYCLASE FAMILY.
QY	361 SRVMDLKQDMTYIVESSAILEPLGSPCVDRLEDFTGRLKLSDIPHNAIRDVVLGEQR 420	CC	
Db	361 SRVMDLKQDMTYIVESSAILEPLGSPCVDRLEDFTGRLKLSDIPHNAIRDVVLGEQR 420	CC	This SWISS-PROT entry is copyright. It is produced through a collaboration between the Swiss Institute of Bioinformatics and the EMBL outstation - the European Bioinformatics Institute. There are no restrictions on its use by non-profit institutions as long as its content is in no way modified and this statement is not removed. Usage by and for commercial entities requires a license agreement (see http://www.isb-sib.ch/announce/ or send an email to license@isb-sib.ch).
QY	421 AQDLGKRRGKLIKATLEAQHAQALEBEKKVTVDLGCSIFCEVAOLWQGVQVQARKFSV 480	CC	EMBL; U60835; AAJ17953..1;
Db	421 AQDLGKRRGKLIKATLEAQHAQALEBEKKVTVDLGCSIFCEVAOLWQGVQVQARKFSV 480	DR	PIR; A38297; OYRPA1.
QY	481 TMLFSDIYGFATICSQSPLOVITMENALYTRFDQCGELDVYKETV[SIDAYCAGG]FK 540	DR	InterPro; IPR01054; G_cyclase.
Db	481 TMLFSDIYGFATICSQSPLOVITMENALYTRFDQCGELDVYKETV[SIDAYCAGG]FK 540	DR	Pfam; PF00211; guanylate_cyc_1.
QY	541 ESDTHAVQIALMALKMELSEVMSPHGEPTKMRGLHSSESVFAGVGVKMPYCLFGNN 600	DR	SMART; SM00044; cyCC_1.
Db	541 ESDTHAVQIALMALKMELSEVMSPHGEPTKMRGLHSSESVFAGVGVKMPYCLFGNN 600	DR	PROSITE; PS00452; GUANYLATE CYCLASES 1; 1.
QY	601 VTLANKFESCSVPKINSPOTYRLKDCPGEVTPRSEELPPNPSETPGICHFLDYY 660	DR	PROSITE; PS03025; GUANYLATE_CYCLASES_2; 1.
Db	601 VTLANKFESCSVPKINSPOTYRLKDCPGEVTPRSEELPPNPSETPGICHFLDYY 660	KW	Lysine; CGMP synthesis; Multigene family.
QY	661 QQGTNSKPCQQKKDVGDNANFLGKASGID 690	FT	DOMAIN 480 607 GUANYLATE CYCLASE.
Db	661 QQGTNSKPCQQKKDVGDNANFLGKASGID 690	SQ	SEQUENCE 690 AA; 77566 MW; E4819B2CA4F86401 CRC64;
QY	61 QRKTTSRSRVYLHTLIAESICKLIPPERLNVALQRTLAKHKIKERSRSLERDEFKIAE 120	Query Match	90.0% Score 3232; DB 1; Length 690;
Db	61 QRKTTSRSRVYLHTLIAESICKLIPPERLNVALQRTLAKHKIKERSRSLERDEFKIAE 120	Best Local Similarity 89.1%; Pred. No 4..3e-218; Matches 616; Conservative 39; Mismatches 34; Indels 2; Gaps 2;	

APPENDIX II

Page 85 of Giuili *et al.* with portions of the sequence that differ from the Gencore database sequence underlined by Applicants.

Fig. 2. Nucleotide sequence and corresponding protein sequence of GC-S α .